Homework Assignment 7: Solutions

Some of the important information for OxyContin®[1] given in the homework assignment included the following:

> The text of the packet insert[2] goes on to give the elimination half-life[3] of oxycodone (on average, it is 3.2 hours) and the suggested dosage (one tablet every 12 hours).

1. In the homework assignment, you were asked to find an equation to represent oxycodone[4] plasma concentration in a patient. The patient had been given a tablet of OxyContin® that quickly raised oxycodone plasma concentration to 20 mg/100ml. The half-life of oxycodone in the human body is 3.2 hours. That is, every 3.2 hours the amount of oxycodone in the body (and hence the oxycodone plasma concentration) will halve. This suggests that an equation similar to the exponential functions used to represent radioactive decay in Math Xa would be appropriate to represent the oxycodone plasma concentration of the patient. The initial value will be 20 mg/100ml.

Let t represent the number of hours since a patient was given an OxyContin® tablet and $M(t)$ represent the oxycodone plasma concentration. Then:

$$M(t) = 20 \cdot \left(\tfrac{1}{2}\right)^{\frac{t}{3.2}} = 20 \cdot (0.805245166)^t.$$

2. To obtain the oxycodone plasma concentration twelve hours after the patient was given the OxyContin® tablet, you can substitute $t = 12$ into the equation from Question 1. This gives an oxycodone plasma concentration of:

$$M(t) = 20 \cdot \left(\tfrac{1}{2}\right)^{\frac{12}{3.2}} = 20 \cdot (0.805245166)^{12} = 1.4865 \text{ mg/100ml}.$$

3. A possible graph of oxycodone plasma concentration versus time is shown in Figure 1 below. Note that the places where the graph "jumps up" correspond to times when the patient receives a new OxyContin® tablet, which increases the oxycodone plasma concentration by 20 mg/100ml. Note also that "open" and "closed" dots have been used to indicate the end-points where the graph "jumps up." Which end-points should be open and which end-points should be closed is a matter of debate. You will not be penalized if you reverse the locations of the

---

[1] OxyContin® is a registered trade mark of Purdue Pharma L.P. Any reference to OxyContin® in this document that does **not** include the symbol ® reflects an omission of this symbol in the original document quoted.

[2] Source: http://www.purduepharma.com/IP/Oxycontin.html

[3] This is the amount of time that it takes for a person's body to eliminate half of the amount of oxycodone present in the body. This is a lot like the "half life" in a radioactive decay problem.

[4] Oxycodone is the active ingredient in the prescription medicine OxyContin®.

"open" and "closed" end-points. The only thing that you might be penalized for is making all of the end-points "closed" end points, which would prevent oxycodone plasma concentration from being a function of time.

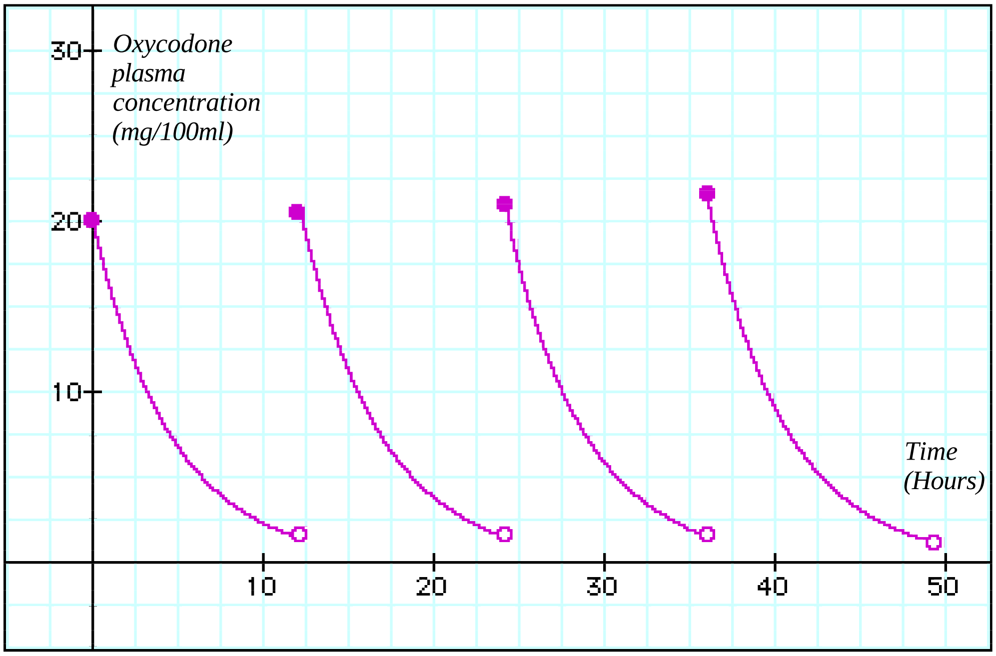

Figure 1

4. The completed table is shown below.

Time since OxyContin® treatment started (hours)	0	12	24	36	48	96	144	192
Oxycodone Plasma Concentration (mg/100ml)	20	21.4865	21.5967	21.6052	21.6058	21.6058	21.6058	21.6059

The entries that could not be obtained from the graph were calculated using the summation formula for a geometric series. To see how this was done, consider the following table which shows how the oxycodone plasma concentration can be expressed as a function of the number of OxyContin® tablets that the patient has taken.

Number of OxyContin® tablets taken	Oxycodone plasma concentration (mg/100ml)
1	20
2	20 + 20·(0.074325)
3	20 + 20·(0.074325) + 20·(0.074325)^2
4	20·(0.074325) + 20·(0.074325)^2 + 20·(0.074325)^3

The pattern that seems to be established here is that immediately after the patient has taken the N^{th} OxyContin® tablet, the oxycodone plasma concentration is given by:

$$20 + 20 \cdot (0.074325) + 20 \cdot (0.074325)^2 + .. + 20 \cdot (0.074325)^{N-1} = \frac{20 \cdot \left[1 - (0.074325)^N\right]}{1 - 0.074325}.$$

5. If the OxyContin® treatment is continued indefinitely, then this could be represented mathematically by imaging that the number of doses of OxyContin® given to the patient, N, is a very large number. The largest possible oxycodone plasma concentration will be obtained as $N \to \infty$. To establish whether or not a patient who continues to take an OxyContin® tablet every 12 hours for an indefinite period of time is at any risk of exposure to a lethal dose of oxycodone, we can use limits to determine what the oxycodone plasma concentration of the patient will eventually end up being.

To do this, we let $N \to \infty$ in the equation:

$$\textit{Oxycodone plasma concentration} = \frac{20 \cdot \left[1 - (0.074325)^N\right]}{1 - 0.074325}.$$

The only part of this equation that is influenced by the value of N is the terms in the numerator:

$$(0.074352)^N.$$

As $N \to \infty$, this gets closer and closer to zero. Therefore the maximum oxycodone plasma concentration that the patient is exposed to is:

$$\textit{Maximum oxycodone plasma concentration} = \frac{20}{1 - 0.074325} = 21.60586557 \text{ mg/100ml}.$$

According to the homework assignment, the lethal dose of oxycodone is estimated[5] to be between 100 mg/100ml and 200 mg/100ml. As 21.6058 mg/100ml is far beneath this range, the patient should be perfectly safe.

Extra Credit:

The most sensitive individuals (to oxycodone poisoning, at least) will experience oxycodone poisoning and (possibly) respiratory arrest when their oxycodone plasma concentration reaches 100 mg/100ml.

Let M_0 represent the oxycodone plasma concentration that an OxyContin® tablet is designed to deliver. Based on the work in Question 5, the maximum oxycodone plasma concentration that a patient would eventually be exposed to if one OxyContin® tablet is taken every 12 hours is:

$$\textit{Maximum oxycodone plasma concentration} = \frac{M_0}{1-0.074325}.$$

To find out what the minimum level of oxycodone plasma concentration that an OxyContin® should deliver in order to *eventually* cause a lethal oxycodone plasma concentration, you can set this expression equal to 100 mg/100ml and solve for M_0. Performing this calculation gives:

$$M_0 = 100 \cdot (1-0.074325) = 92.56745 \text{ mg/100ml.}$$

Purdue Pharma L.P. warn physicians **not** to prescribe the M_0 = 80 mg/100ml and M_0 = 160 mg/100ml OxyContin® to patients who are not opioid tolerant[6].

There seems to be clear reason for this policy in the case of the M_0 = 160 mg/100ml OxyContin® - if given to a patient who is not opioid tolerant, the patient will eventually accumulate a lethal oxycodone plasma concentration in their body and get into serious medical problems, possibly including death due to respiratory arrest.

The warning on the M_0 = 80 mg/100ml OxyContin® is probably an effort on the part of Purdue Pharma L.P. to leave a reasonable margin for error. Although according to these calculations there is (in theory) no danger of accumulating a lethal oxycodone plasma concentration in their body when M_0 = 80 mg/100ml OxyContin® is prescribed even to an opioid intolerant patient, it should be remembered that the lethal dose is *estimated*. I doubt that Purdue Pharma L.P. wants anyone to die as a result of an OxyContin® prescription, so they have included a margin for possible error by warning physicians not to prescribe the M_0 = 80 mg/100ml OxyContin® to anyone who could conceivably accumulate a lethal oxycodone plasma concentration in their body.

---

[5] Source: http://ash.xanthia.com/ The oxycodone plasma concentrations given are for people who are not accustomed to opiates. For people who are tolerant of or accustomed to opiates, these lethal doses may be higher. This dosage is called the LD-50. "LD-50" stands for "Lethal Dose 50%" which means the dose at which 50% of people who were exposed would be expected to die. This figure is estimated because the FDA generally does not permit clinical trials in which a pool of patients are exposed to steadily higher levels of the substance until 50% of them are dead.

[6] Source: http://www.purduepharma.com/IP/Oxycontin.pdf